

# Utah Science

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# Utah Science

A Publication of the Utah Agricultural  
Experiment Station at Utah State University

Volume 70 Issue 1    Fall/Winter 2016

**UtahStateUniversity**  
AGRICULTURAL EXPERIMENT STATION



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Research on topics like heart arrhythmia, cancer, and disease caused by West Nile, Zika and influenza viruses may seem like tasks for scientists at a medical school. But important breakthroughs in medicine begin with basic research that happens in cell culture and in animal models.

Understanding and improving human health is just one area in which Utah State University faculty are at work with support from the Utah Agricultural Experiment Station. The discoveries they make have had far-reaching impacts, and we are increasingly focused on the

many vital connections between the health of ecosystems, animals and people.

In this issue of Utah Science are stories of how goats may be important to understanding the most common type of heart disease, how your physiology may have a lot to do with bacteria in your gut, and how a team of our researchers have played a role in providing the world with medicines and vaccines and are at work to counter emerging diseases caused by Zika and other viruses.

This fall, the Utah Agricultural Experiment Station and USU's College of Agriculture and Applied Sciences hosts an international conference that will bring together experts in large animal genetic engineering. These specialized animal models are important in work that may improve livestock production and also help humans hold cancer at bay, allow people with cystic fibrosis to breathe freely, or lead to treatments for neurological damage.

Our faculty are also organizing a second Utah One Health Symposium to focus on the interrelationships of animal health, human health and the environment. Understanding human, environmental and animal health are not distinct and separate undertakings. We are proud of the work our faculty and students do on research farms and in labs and classrooms, all aimed at improving lives.

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## Ken White

**Director, Utah Agricultural Experiment Station**



### **ON THE COVER**

*Illustration of the bacillus microorganisms.  
Image by Dmitry Sunagatov.*

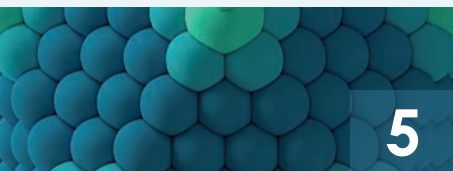
# Utah Science

Volume 70 Issue 1    Fall/Winter 2016



## What's on Your Plate?

When studying cancer in mice, USU researchers are starting with a “Western diet” and finding more connections between diet and health... good and bad.



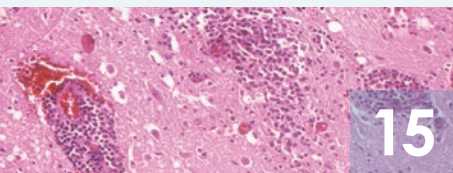
## Uncommon Hamsters Helping Fight Common Viruses

New genetically modified hamsters play an important role in studying human diseases caused by adenovirus, and may also be valuable in studies of Ebola, dengue and hanta viruses.



## Science vs. Viruses

When viruses cause enough damage to make the news, it's rarely “news” to scientists at the Institute for Antiviral Research. Learning how viruses work, and testing drugs to stop them, is what faculty and student researchers have done there since 1977.



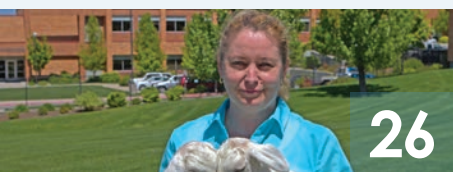
## Mapping Zika Virus Genomes

A team of Utah State University researchers has mapped the genomes of three strains of Zika virus, an important step in understanding the virus and developing strategies to treat and prevent Zika virus infection.



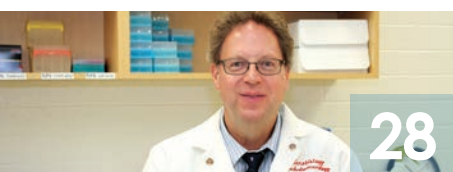
## Our Complicated Relationship with the Microbiome

As many as 1,000 species of microorganisms inhabit in the human digestive tract and have a lot to do with our individual health. But can transferring some of the good bacteria from one gastrointestinal tract to another provide benefits?



## Transgenic Goats May Help Heal Hearts

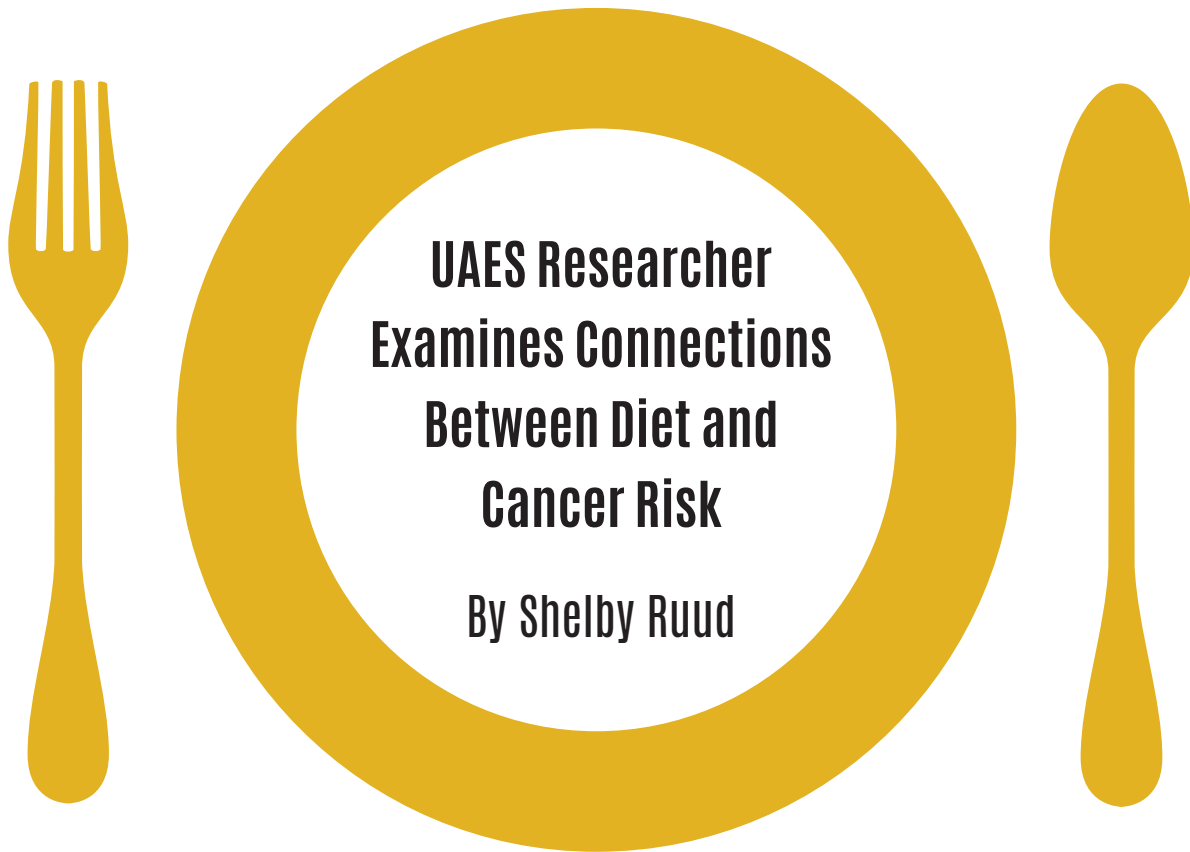
Atrial fibrillation is the most common kind of abnormal heartbeat in humans, and newly engineered goats may help doctors understand why and how to treat it.



## One Health and Emerging Infectious Diseases

Infectious diseases can travel remarkably fast and emerging human diseases increasingly have their origins in wildlife and other animals. Scientists are paying greater attention to connections between the health of people, animals and the environment.

# WHAT'S ON YOUR PLATE?



**S**mall, everyday decisions such as what to put in your grocery cart or which restaurant to eat at may seem insignificant. But in reality, what's on your plate and what's missing from your plate could have more long-term health consequences than previously thought. The Applied Nutrition Research Group, a team of researchers in Utah State University's College of Agricultural and Applied Sciences with a diverse range of expertise, is examining certain health concerns and how they relate to diet. Utah Agricultural Experiment Station researcher and Utah State University Associate Professor Abby Benninghoff and her team are specifically examining how the food we eat impacts the rate and severity of colon cancer.

Scientists have long been interested in studying cancer. Ideally, they would be able to use humans to study the complexities of the disease, but

unless researchers are willing and able to study cancer patients for decades at a time, it's just not feasible for diseases that typically develop later in life. Instead, researchers use mice as models for humans. "This is one of the biggest challenges when we use laboratory animals as surrogates for people," Benninghoff said. "We all know a mouse is not a human. But we can optimize our studies the best that we can and make these models better."

Optimizing animal models to study cancer risk is one aspect that makes this project unique. "Historically, when scientists have looked at cancer in mice, they feed these animals a healthy diet to get them to the optimal level of health," Benninghoff said. "My colleagues and I looked at that practice and said, 'Well, that really doesn't emulate what Americans eat.'" Instead

of following the traditional model, the research team developed a diet for rodents that more closely mimics what the average American is eating: a diet high in fats, high in simple sugars, and lacking many vitamins and minerals.

After implementing the "Western diet" into their studies, Benninghoff's team compared mice on a healthy diet to mice consuming the diet that reflects what Americans eat. Mice on the Western diet had a much higher rate for tumor development in the colon, which didn't surprise Benninghoff and her colleagues. Their findings fit with other epidemiological research that points to poor diet being a huge risk factor for colon cancer. The next step for the research team is to figure out why this is the case.

The team is examining the gut microbiome, which is the collection of microorganisms in our stomachs. The





*Utah State University Associate Professor and Utah Agricultural Experiment Station researcher Abby Benninghoff.*

human gut is host to an ecosystem of more than 100 trillion bacteria. This microbiome plays a big role in the body's digestive system—it metabolizes indigestible compounds, it produces energy and it provides defense against pathogens. With the gut microbiome playing all these roles, it's possible that protection against colon cancer may be dictated in part by the gut microbiota population. In fact, the gut microbiomes of patients with gut inflammation are noticeably different from healthy ones, with consistent observations of less diversity and richness of the microbial community. Understanding specific gut microbiome patterns that are associated with disease risk could provide new targets for risk reduction or therapy.

The role of micronutrients has also been a point of interest for the research team. Benninghoff said many people think of poor food choices and associate them with macronutrients like fats. Benninghoff's work suggests that a lack of micronutrients, including vitamins and minerals, plays a much

more substantial role in cell health and increased cancer risk.

"The role of micronutrients was a bit of a surprise, based on what we'd previously thought," Benninghoff said. "But when you look at how these micronutrients have a central role in maintaining proper cell functions, it's not really a surprise at all." Benninghoff's team is now working on understanding which micronutrients play a key role in the long-term health of the intestine.

It's not all bad news, however. Instead of focusing solely on factors that exacerbate diseases, the research team is also interested in foods that do the opposite and reduce the risk of cancer. Bioactives are chemicals naturally found in certain foods, but they're not the standard vitamins and minerals. These chemicals can interact with our cells and promote health, prevent inflammation and block some pathways that might lead to cancer. The Applied Nutrition Research Group is studying bioactives in foods such as broccoli, green tea, tart cherries—even purple corn.

## AWARD WINNING

*In 2015 and again in 2016, Benninghoff and her collaborators, including USU toxicologist, Professor Roger Coulombe, won the Multi-State Research Award from the Western Association of Agricultural Experiment Station Directors. This award recognizes excellence within a collaboration that includes representatives from several states across the nation.*

*"The work that [these] researchers have conducted has increased our understanding of the complex relationship between bio-active dietary chemicals and human health, which is of paramount concern to consumers, agricultural producers, food processors, health professionals, and policymakers charged with maintaining a safe and nutritious food supply."*

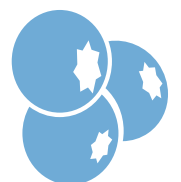
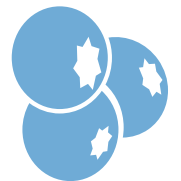
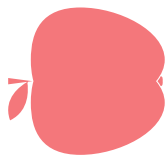
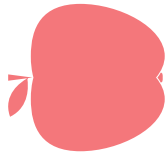
*The team includes researchers from 18 other universities and government research agencies.*

## Contact Info:

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"The best advice I can give for anyone who wants to reduce their cancer risk and improve their overall health is to make their plate as colorful as possible," Benninghoff said. "A lot of foods that have the healthy bioactives are brightly colored, so look for the vibrant greens, blues and reds."



And the benefits of a colorful plate could have implications far into the future. Using the mouse models for their research, the team is examining ancestral exposure to diet. They are interested in whether or not someone's poor food choices could negatively affect the health of their offspring generations into the future. This field of research is called epigenetic inheritance and examines the epigenome, which is another layer of genetic code similar to the genome, and how it can be inherited across generations. The research team believes that this could be a key to understanding cancer risk.

"People are already recommended to eat well," Benninghoff said. "If we tell people that your children, or your grandchildren, or your great-grandchildren could suffer because of your diet choices, I think it could lend weight to the nutrition recommendations that doctors give their patients."

Benninghoff and other team members, including USU researchers Korry Hintze, Michael Lefevre, Robert Ward and Jeffery Broadbent and graduate student Sumira Phatak, are several years into this project and are beginning to accumulate the results of their various studies. Benninghoff said one of the most rewarding parts has been tabulating the data, examining the results and asking "What did we learn?". The team is always considering where they can take this project next.

"When I was a graduate student, my biggest fear was that I'd run out of ideas," Benninghoff said. "But it's been the complete opposite. There's so much I want to do in terms of research. The ideas are absolutely not in short supply." 





# UNCOMMON HAMSTERS HELPING FIGHT COMMON VIRUSES

By Nancy Solomon & Lynnette Harris



Using an animal model they developed, Utah State University and Saint Louis University researchers have identified a strategy that could keep a common group of viruses called adenoviruses from replicating and causing sickness in humans.

The study, published in the Aug. 20 issue of *PLOS Pathogens*, is the first to report use of a genetically modified Syrian hamster that may prove important in studying other dangerous viruses.

"The adenovirus can cause colds and infections in the eyes and respiratory system and generally are not serious," said William Wold, co-senior author of the paper and chair of molecular microbiology and immunology at Saint Louis University. "However, like many other viruses, adenovirus can replicate at will when a patient's immune system is suppressed. Adenovirus

can become very dangerous, such as for a child who is undergoing a bone marrow transplant to treat leukemia."

Wold and his colleagues found that Type 1 interferon is critical to preventing adenovirus from multiplying. Interferon is a protein and part of the body's immune response that fights against invading pathogens. Cells that are infected by a virus release interferon to signal nearby non-infected cells to be on alert to fight the invading virus.

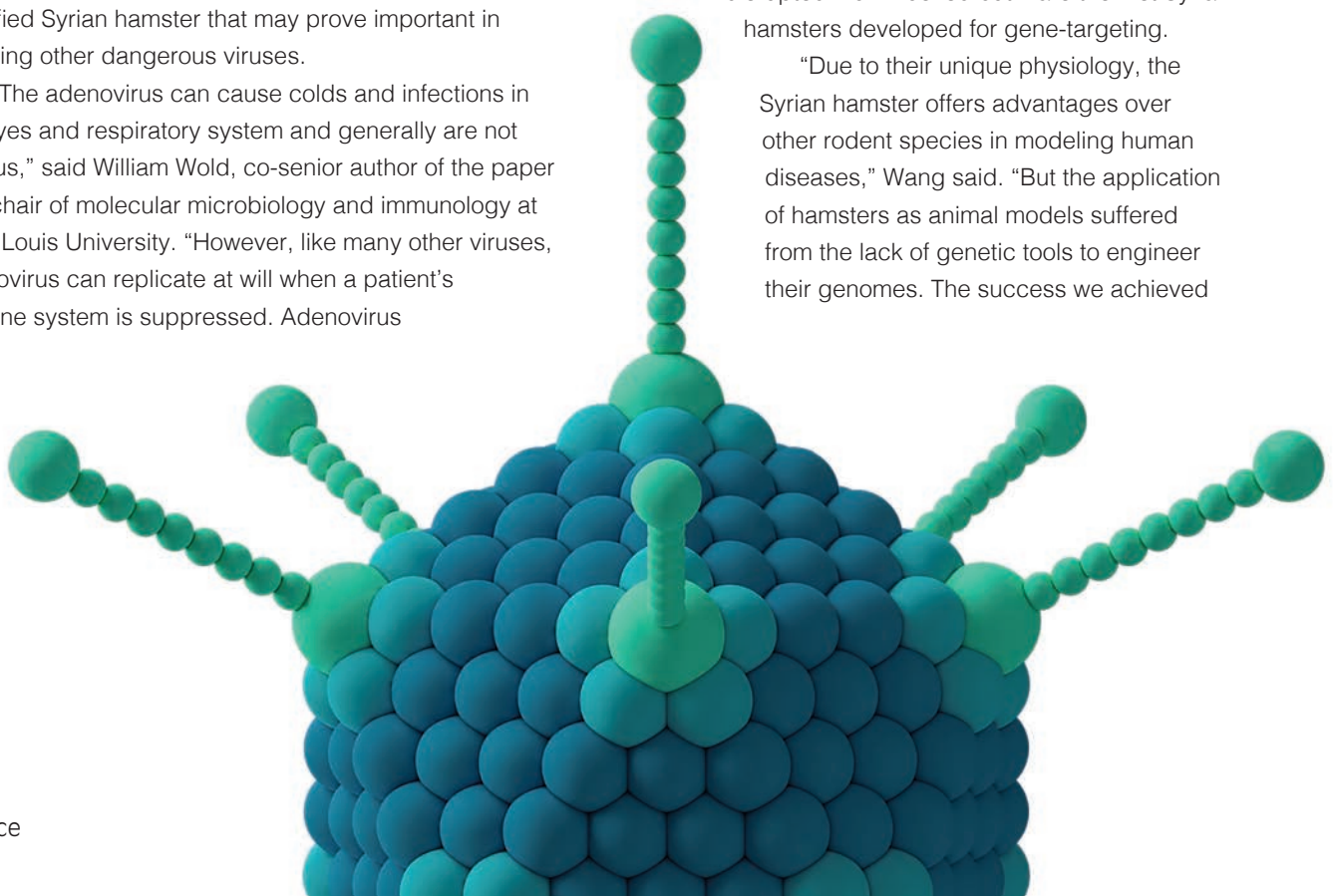
Researchers led by Zhongde Wang, associate professor of veterinary diagnostics and infectious diseases in USU's Department of Animal, Dairy and Veterinary Sciences and co-senior author of the paper, turned off the STAT2 gene in a group of Syrian hamsters, which disrupted the Type 1 interferon pathway by interrupting the cascade of cell signaling. The team compared that group with a group of wild-type control animals, both of which had adenovirus. The genetically modified Syrian hamsters had 100 to 1,000 times more virus in their bodies than the control.

"While thousands of papers have been published on the replication of adenovirus in a cell culture model, until now, not much has been understood about the molecular details during adenovirus replication in humans," Wold said.

Wang said, "Besides providing an insight into adenovirus infection in humans, our results are also interesting from the perspective of the animal model: the STAT2 knockout Syrian hamster may also be an important animal model for studying other viral infections, including Ebola, hanta and dengue viruses."

The animals used in the study with the STAT2 gene disrupted – or knocked out – are the first Syrian hamsters developed for gene-targeting.

"Due to their unique physiology, the Syrian hamster offers advantages over other rodent species in modeling human diseases," Wang said. "But the application of hamsters as animal models suffered from the lack of genetic tools to engineer their genomes. The success we achieved





with gene-targeting in the Syrian hamster provides the opportunity to create genetically engineered hamsters as models for many of the human diseases for which there are either no existing animal models or models with severe limitations.”

Previously, Wold led a research team that identified the Syrian hamster as an appropriate animal model to study adenoviruses because human adenovirus replicates in these animals, causing sickness that is similar to that seen in humans. Wang said the work reported in PLOS

Pathogens is significant because there was previously no animal model for studying adenovirus replication without using drugs to suppress animals’ immune systems. The study provides a basis for using the STAT2 Knockout hamsters to understand infection and to develop antiviral drugs and vaccines.


In addition, Wang said, a variety of adenoviruses – known as oncolytic adenoviruses – preferentially infect and kill tumor cells are of great interest in treating human cancers, but none of the small animal models currently in use allows adenoviruses to replicate effectively.

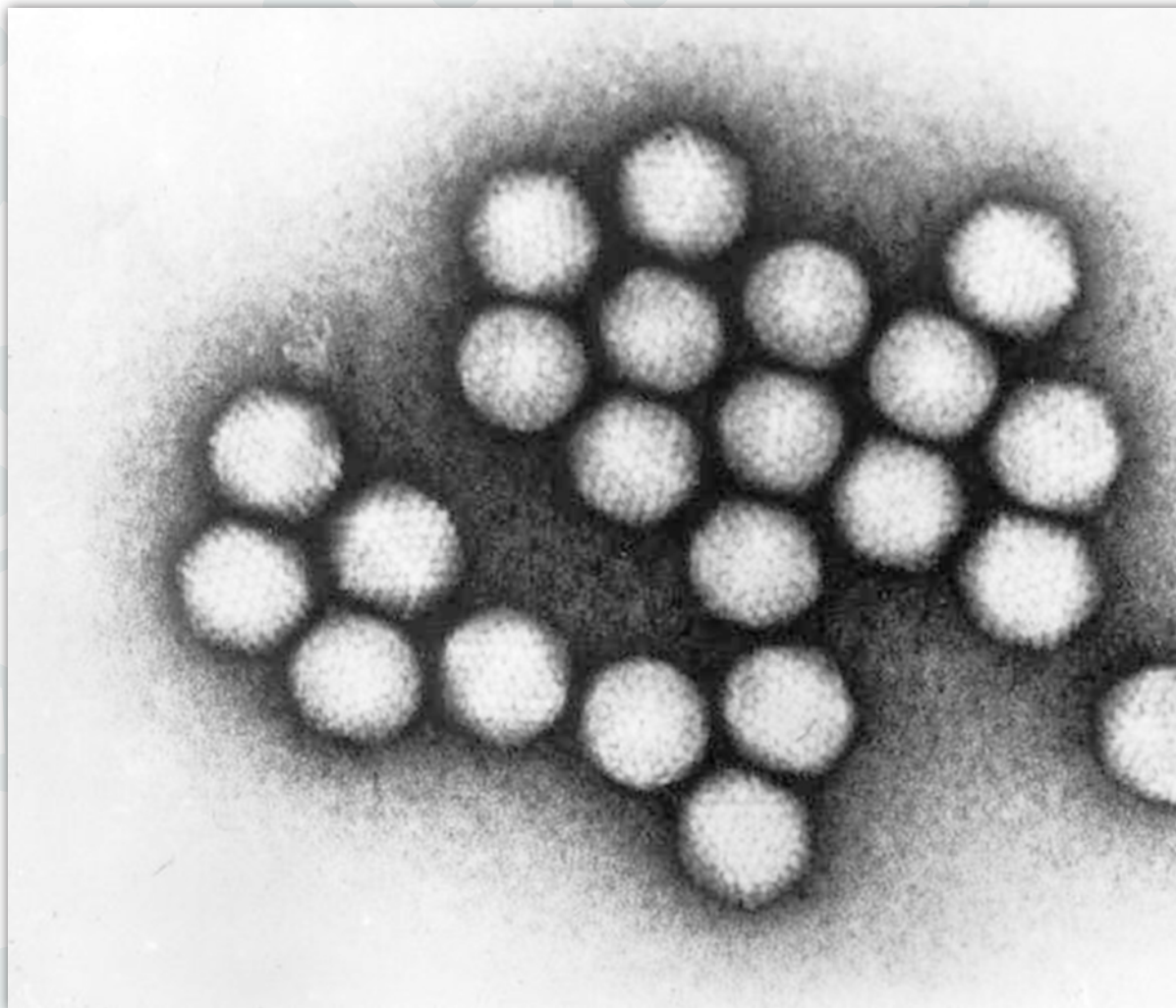
Because the newly developed hamsters do permit the virus to replicate, they open a door to new methods of developing and studying cancer-fighting adenoviruses.

Other members of the research team include Karoly Toth, Baoling Ying, John E. Sagartz, Jacqueline F. Spencer and Ann E. Tollefson, Saint Louis University; Sang R. Lee and Wang, Utah State University; and Il-Keun Kong, Gyeongsang National University, Jinju, South Korea.

Wang’s research group made a technical breakthrough in 2013 with gene targeting in the golden Syrian hamster and produced the world’s first genetically

engineered hamsters, in collaboration with Kong’s group in South Korea. The initial advancement was also supported by technical contributions from two other laboratories at USU led by Ken White, animal scientist and dean of the College of Agriculture and Applied Sciences, and Thomas Bunch, emeritus professor of animal science.

The paper is available on the PLOS Pathology website at: <http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1005084> 



**Top Left:** Associate Professor Zhongde Wang.

**Bottom Left:** Schematic of adenovirus: National Institutes of Health.

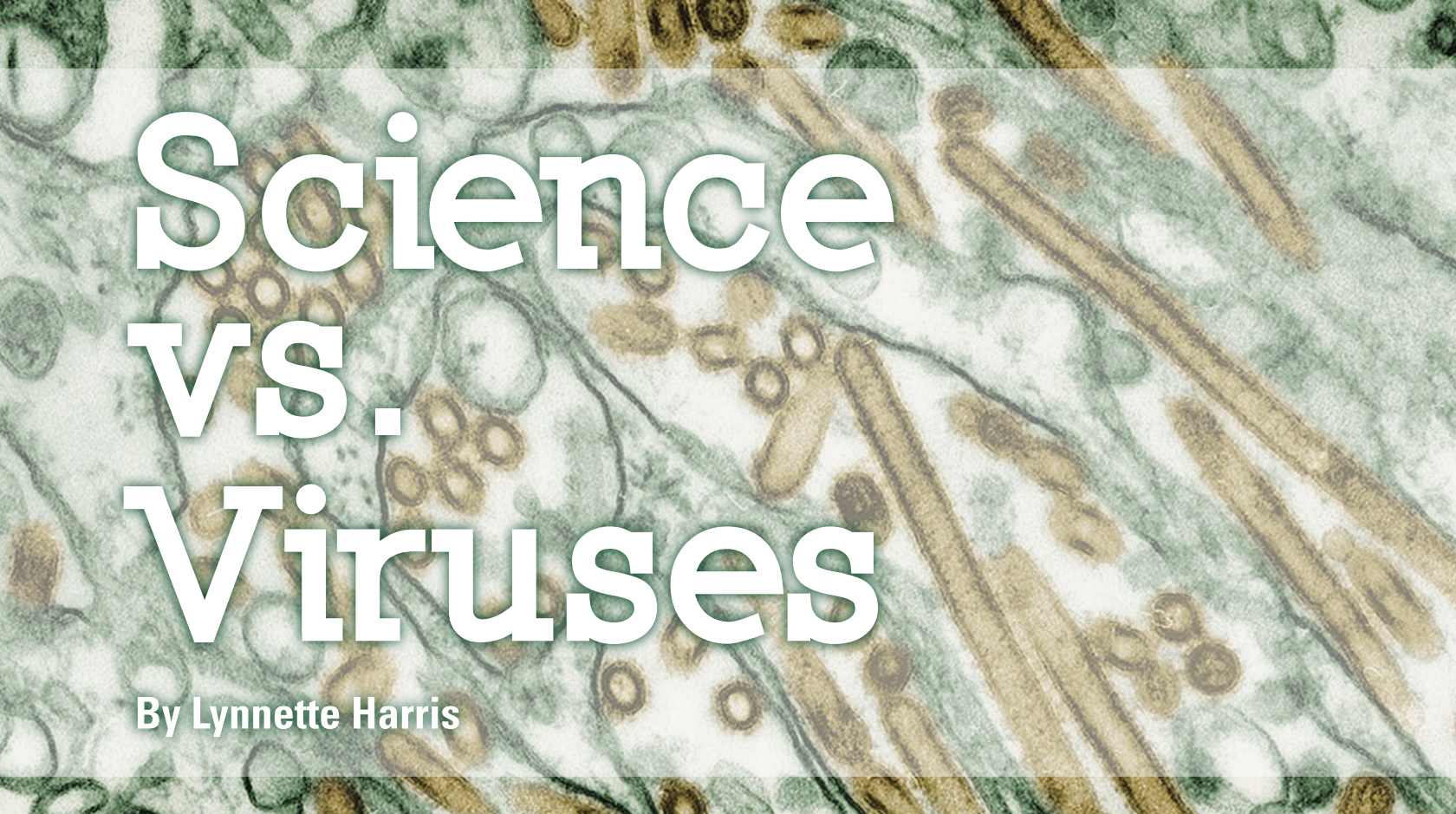
**Above:** Transmission electron micrograph (TEM) of adenovirus virions. Photo courtesy of CDC/ Dr. G. William Gary, Jr.



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# Science vs. Viruses

By Lynnette Harris

**W**hen viruses cause disease and make local, national and international news, most of us react with some anxiety, take precautions to prevent or limit contact with the virus and adopt a heightened awareness of symptoms. When Professor John Morrey and his colleagues at Utah State University's Institute for Antiviral Research hear and read stories of dangerous emerging or recurring diseases, it's rarely "news" to them, but it brings a renewed urgency to their work.

"When people ask 'How's your work going?' I tend to always look ahead and think of the challenges and needs instead of looking back and seeing our successes, and we've had some great successes," Morrey, the institute's director, said. "There is always more to do. We always need more data, more ideas, and there are always more grants to write, more papers to write, more things to understand."

Morrey can be forgiven for focusing on the challenges. When your work is studying viruses, you may experience some exciting breakthroughs, but you are never really finished.

The institute's team includes seven lead investigators who are Department of Animal, Dairy and Veterinary Sciences faculty members, six PhD-level senior research associates, and several full-time and student technicians. The viruses and diseases they study—think influenza, hanta, dengue, West Nile, chikungunya, SARS and Zika—could comprise an international "Most Not Wanted" list. The researchers don't discover new drugs, they test possible treatments in cell culture and animal models, investigate basic mechanisms of

how viruses function and cause disease and search for ways to disrupt a viruses' particular ability to do damage.

Doing basic biological research is important, but not filled with daily, flashy "Eureka" moments. However, without basic research the development of drugs, vaccines and tests for diseases would never happen. For example, the researchers' discovery of the ways in which viruses like West Nile infect the brain stem and cause respiratory problems is important because it gives drug developers better targets for treatments and vaccines. Morrey likened it to being a guide.

"If you go fishing in a large lake you need to go where the fish are," he said. "By discovering that West Nile and other neurological viruses can cause respiratory deficits, particularly with lesions in the spinal cord and brain stem, we've helped get scientists in the part of the lake where they can be productive."

The team reached a notable milestone this year, surpassing \$107 million in grants and contracts since the institute was founded in 1977 and led by Robert Sidwell, now an emeritus professor. But don't go looking for them in a gleaming, high-profile research center. Most of their work goes on in secured laboratories with up-to-date equipment and protocols, but the modest surroundings belie the caliber of research that goes on there every day.

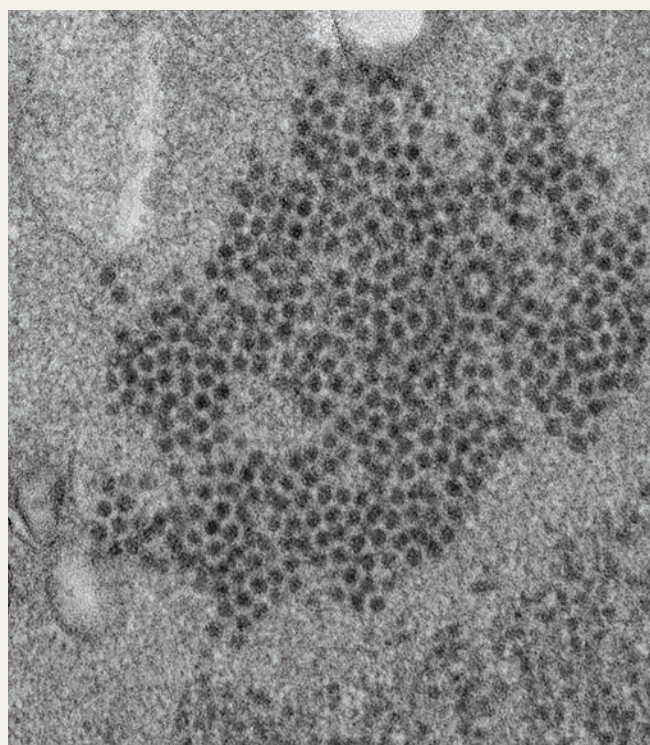
To Morrey, surpassing the \$100 million mark in grant funding represents the group's collective work and "the many pharmaceuticals in which we have played a part, and seeing them used by people around the world to fight viral disease and improve lives."



## VIRUSES IN THE LAB

Studying viruses in cell culture can tell scientists a great deal, but animal models play crucial roles in understanding viruses and testing possible treatments. Research Associate Professor Justin Julander explained that the complexity of the body, whether human, mouse or hamster, can't be replicated in a petri dish or flask. Experiments in cell culture are important for targeting and measuring some responses, but cultures don't replicate nearly countless variables like neuron function, respiration and immune response. Studies in animal models are important steps on the path to treating humans and running complex and expensive clinical trials of vaccines and drugs in humans. However, mice and hamsters are not naturally susceptible to virus strains that infect humans.

Associate Research Professor Bart Tarbet pointed out that a key reason the researchers can do their work is the institute's colony of mice with specific genes "knocked out" to make them receptive to virus infection. Colleagues at USU also recently developed a first-of-its-kind, genetically engineered hamster that is proving valuable in the search for Zika virus treatments. Tarbet's lab works with genetically engineered mice in the search for a new model for



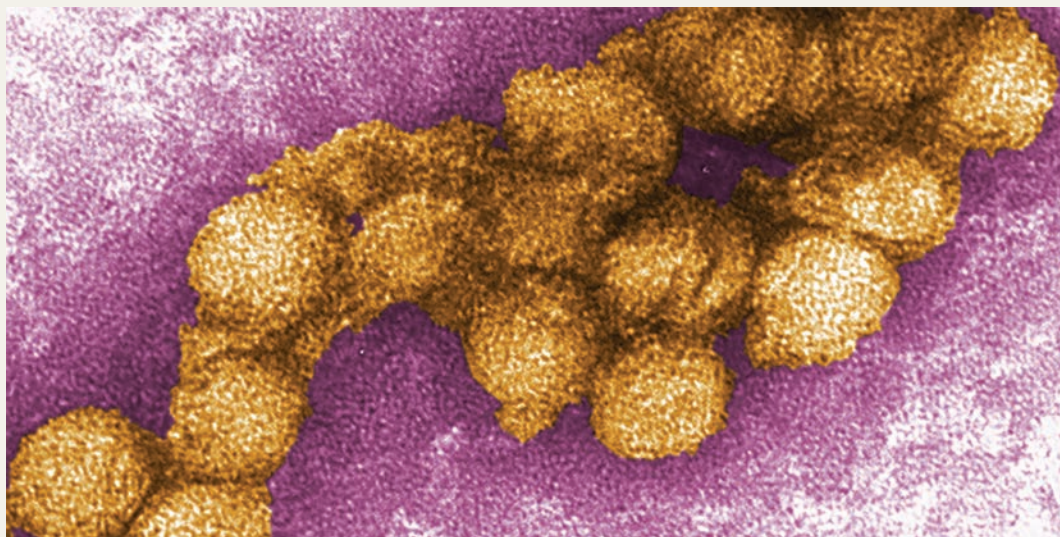
EV-D68 cases. Most troubling though was that some people developed a polio-like neurological disease, not just the usual respiratory infection that causes problems primarily

for the very young, the very old and people with asthma. With funding from National Institutes of Health (NIH), Tarbet's lab is focused on developing a reliable testing model, and will follow that with 2 years of evaluating possible treatments.

It's important to note that most drugs don't make the cut from cell culture to tests in animal models and even fewer progress to clinical trials.

"For example, 3 years ago the institute screened

over 10,000 drugs to treat influenza in cell culture," Tarbet said. "Of those, fewer than 2 percent showed activity against the virus and just those few were considered for testing in animal models."



**Left:** Colorized transmission electron micrograph of avian influenza A H5N1 viruses (seen in gold) grown in MDCK cells (seen in green). Photo Credit: Cynthia Goldsmith, Centers for Disease Control and Prevention

**Right:** This photo shows an electron micrograph of a thin section of EV-D68, showing the numerous, spherical viral particles. Image source: Cynthia S. Goldsmith and Yiting Zhang, CDC

**Above:** This is a transmission electron micrograph (TEM) of the West Nile virus (WNV). See PHIL 2290 for a black and white version of this image. Photo Credit: Cynthia Goldsmith, Centers for Disease Control and Prevention

treatments of enterovirus D68 (EV-D68). The virus is one among a family that includes polio and more than a 100 non-polio viruses, and has caused illness that the Centers for Disease Control and Prevention has tracked since 1987. But in 2014, there was a spike in the number and severity of



Julander said because it costs millions of dollars to develop a new drug and bring it to market, the institute's team feels fortunate to be doing work at the university where they are not tied to a company's bottom line. Morrey added that some people believe that any scientist who associates with the pharmaceutical industry has been bought off.

"The fact is, the data we generate is completely unbiased, and whether it's good news or bad news for a particular treatment, they get whatever we learn," Morrey said.

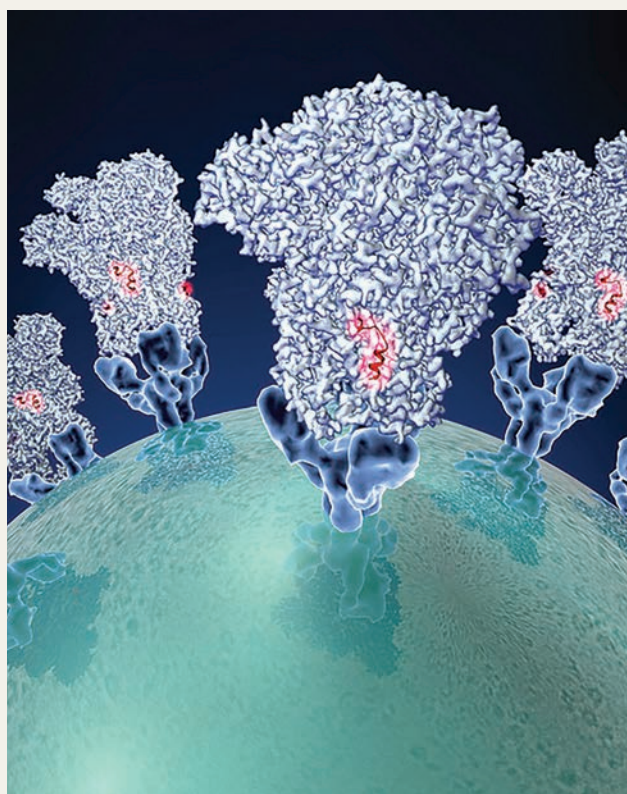
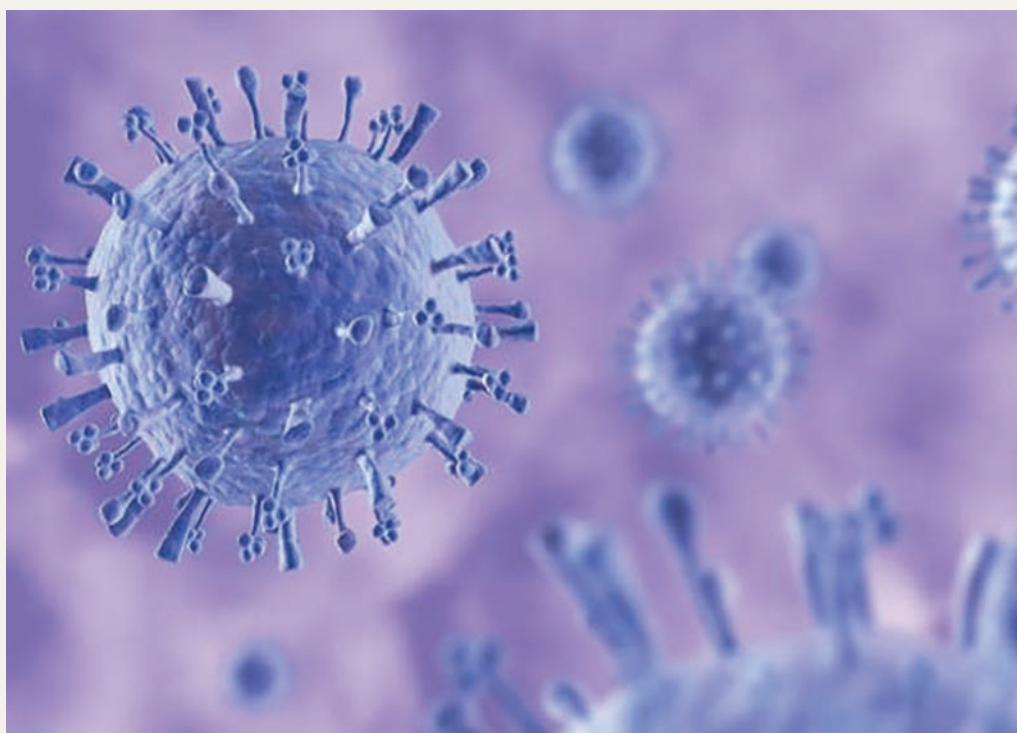
## CHALLENGES: PAST AND PRESENT

Battling established and emerging virus diseases is a complicated task for many reasons, some due to the nature of the viruses themselves and some because of the actions of people and animals they affect.

"One of the things that makes viral infections so difficult to treat is that viruses rely on the host's cells for growth," Morrey said. "It is the biggest challenge in developing therapies. Viruses rely on the machinery of the cells they infect. That is not the case with bacterial infections because, with a couple of exceptions, bacteria live outside our cells. So some of the conceivable approaches to eliminating a virus also eliminates the host's cell. Virologists like to do better than that and find very specific, unique viral processes that can be targeted so the cell is not harmed, but the virus is eliminated."

Another vexing characteristic of viruses is their ability to mutate, adapting to new surroundings or drug challenges. This ability allows viruses to expand their ranges, cause infection in new ways and become less or more virulent. It also means that once researchers have characterized a virus and how it works, the virus may have already changed. When viruses change in ways that make them more virulent or easier to transmit, the results can be devastating.

Such was the case with Spanish flu in 1918-1919.



**Top:** Model of H1N1 Influenza virus.

**Above:** The illustration shows a viral membrane decorated with spike glycoproteins; highlighted in red is a potential neutralization site, which is a protein sequence that might be used as a target for vaccines to combat viruses such as MERS-CoV and other coronaviruses. Photo Credit: David Veessler, University of Washington

**Right:** The core of the USU's Institute for Antiviral Research are faculty members (left to right, front) Justin Julander, Dale Barnard, Craig Day, (center) Don Smee, John Morrey (back) Brian Gowan, Bart Tarbet.



That strain of influenza—a subtype of avian influenza H1N1—became more deadly and easier to spread, explained Research Professor Dale Barnard. As a result, 20-40 million people died in a worldwide pandemic, far more than the 17 million who were killed in combat in that final year of World War I.

“Sometimes research can be driven by fear and media attention,” Barnard said. “But the experience of Spanish flu is one reason we are so vigilant and put great effort into understanding newly emerging viruses. We want to be able to intervene before something like that happens again.”

Another public health challenge is that people are very mobile today and can transport viruses to new locales with greater speed. Barnard said that prior to the mid-20th century the geographic range of two viruses he studies, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), would have been quite limited. But today planes transport passengers and viruses between countries and regions of the world in a matter of hours.

Barnard and his team are at work screening antiviral drugs for effectiveness against MERS, coronavirus infections and respiratory syncytial virus (RSV) among other respiratory viruses. He observed that there are tools for drug development and testing that make the work faster than it

was at the start of his career, but drug discovery hasn’t accelerated as rapidly as viruses’ abilities to spread.

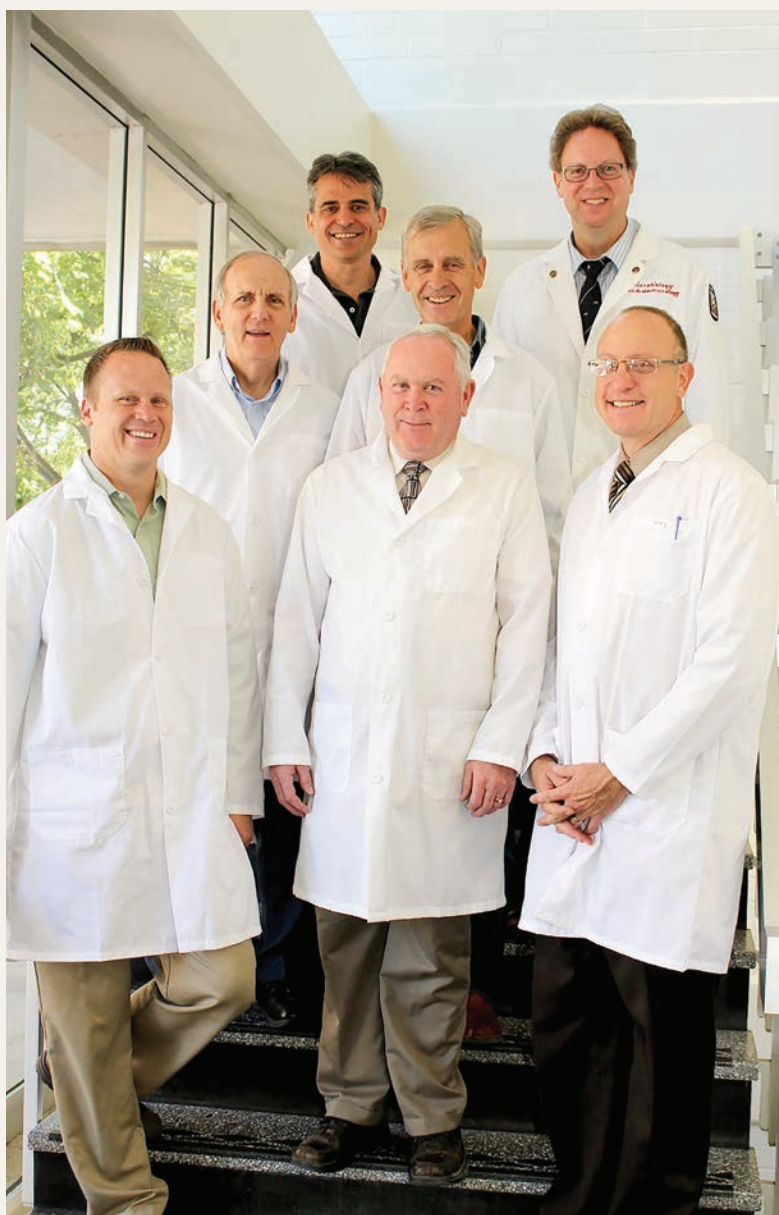
Changing climate presents another challenge. Many virus-caused diseases are zoonotic, meaning they arise in animals and spread to humans. Mammals, birds and insects, like the now-famous, Zika-carrying *Aedes aegypti* mosquito, act as vectors for spreading viruses. Their ranges may expand or at least change as the climate and their habitats change.

## ZIKA VIRUS IN THE NEWS

By the time stories about Zika virus hit mainstream media in the U.S. this spring, the Institute for Antiviral Research had already been at work with the virus for several months with funding from the NIH. The team of researchers has since demonstrated in mice and hamsters that the virus does transfer from mother to fetus and cause growth restriction and other developmental anomalies at various times during fetal development. That gives the team good models for studies, including evaluation of a possible vaccine and use of therapeutic antibodies that may stimulate the immune system to attack the virus.

Julander, who leads the institute’s Zika virus research, said they have seen size differences and ocular deformities in mouse pups born to dams that were infected with Zika virus. It appears that infection during the first trimester of pregnancy is the most troubling.

“We previously found with West Nile virus that infection in the first trimester is the most critical time for abnormal



fetal development and we see the same thing with Zika,” Julander said. “We need a vaccine to protect against Zika virus because more than 80 percent of people who get the virus have no symptoms or develop only a mild illness. The key to fighting most viral infections is starting treatment when the viral load is small. No one is going to go to the doctor because they got a mosquito bite, so by the time someone feels symptoms the virus has become well established.”

Though both West Nile and Zika virus are spread by mosquitoes and can cause neurological disease, Morrey said there are key differences between two. Zika virus can be spread from one infected person to other people via mosquito bites. It can also be sexually transmitted. West Nile does not spread in those ways.

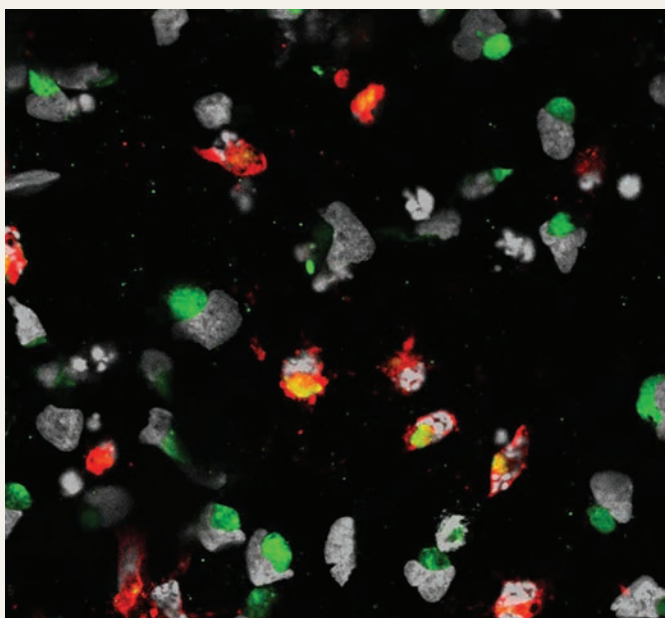
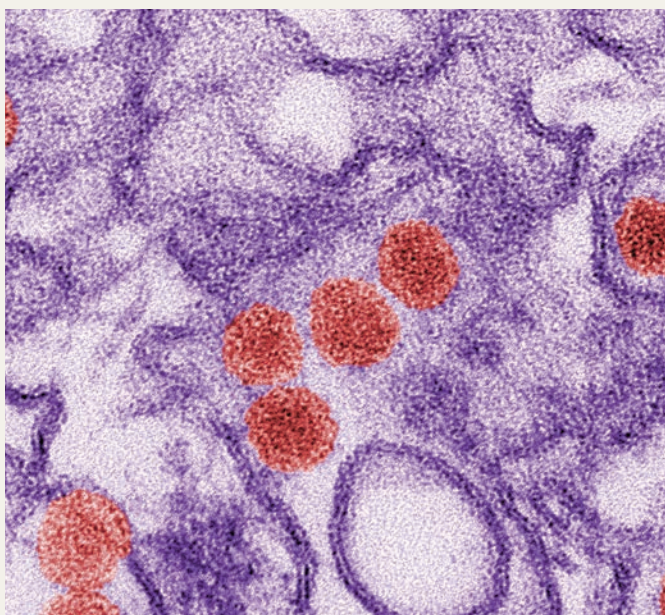
“Zika can mutate, and it does” Morrey said. “It’s very interesting because you can get a blood sample, but can’t culture it by some of the expected cell culture techniques because its genes have already changed in the time it took for viremia to occur (the virus to develop in the bloodstream). The viruses actually change when they go from mosquito to human and from human to mosquito, but Zika does this in a more obvious way.”

## WHAT’S NEXT?

The faculty members at the core of the institute’s research team have “self-selected” to focus on specific kinds of virus infections. But the relatively small size of the team means ideas easily cross-pollinate, and discussions in lab meetings or in the hallway may lead to new questions, answers and shared expertise. There is no shortage of known viruses on which to focus so the research leaders, technicians and students go on working, networked with the larger scientific community, and always watching for signs that a new virus may be emerging, or a well-known one resurging.

Morrey said one frustration is that the procedure for approving new drugs does not currently work well for fighting emerging diseases. Regulations require that clinical trials include large numbers of people. The problem is that cases of people infected with an emerging disease are often sporadic and geographically far apart, so it is extremely difficult or impossible to include enough people in a single treatment trial.

“It has prevented the development of some drugs that could be useful, but the FDA is bound by law,” Morrey said. “The law needs to be adapted



**Top:** This is a digitally-colored transmission electron micrograph (TEM) of Zika virus, which is a member of the family *Flaviviridae*. Virus particles, here colored red, are 40 nm in diameter, with an outer envelope, and an inner dense core. Image courtesy of CDC/ Cynthia Goldsmith.

**Bottom:** Human neural progenitor cells (gray) infected with Zika virus (green) increased the enzyme caspase-3 (red), suggesting increased cell death. Credit: Sarah C. Ogden, Florida State University, Tallahassee

for emerging diseases like Zika and West Nile virus. It will require the political will to make those changes. It may require loosening some standards in order to accomplish the studies, and no one wants to be blamed for doing something that might not be safe.” 🟡



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# Countries & Territories with Active Zika Virus Transmission

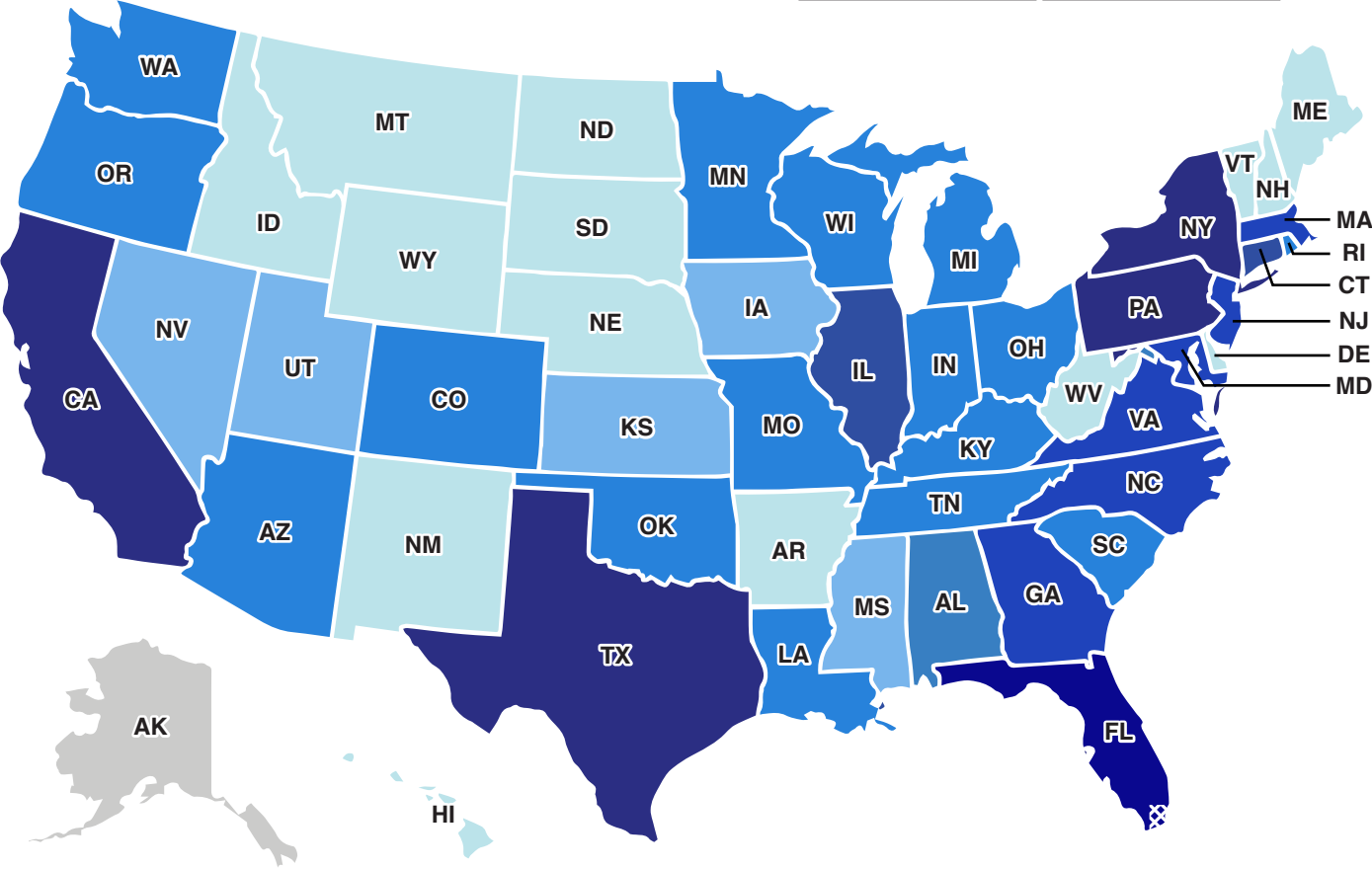
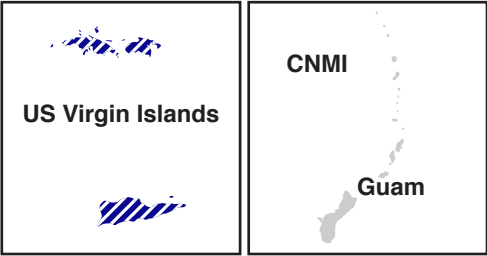
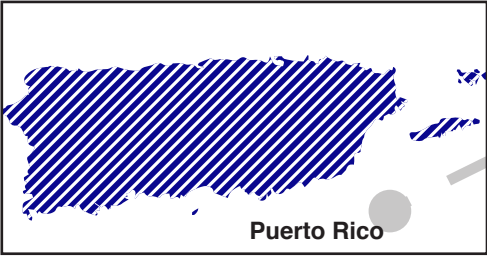
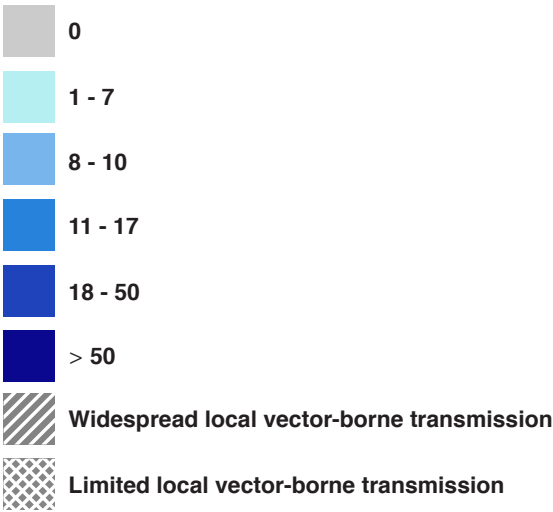


*\*Data from Centers for Disease Control and Prevention*

# Zika Cases Reported in the United States

## States and Territories Reporting Zika Virus Disease

Solid shading represents travel-associated cases only



\*Data from Centers for Disease Control and Prevention





# Mapping Zika Virus Genomes

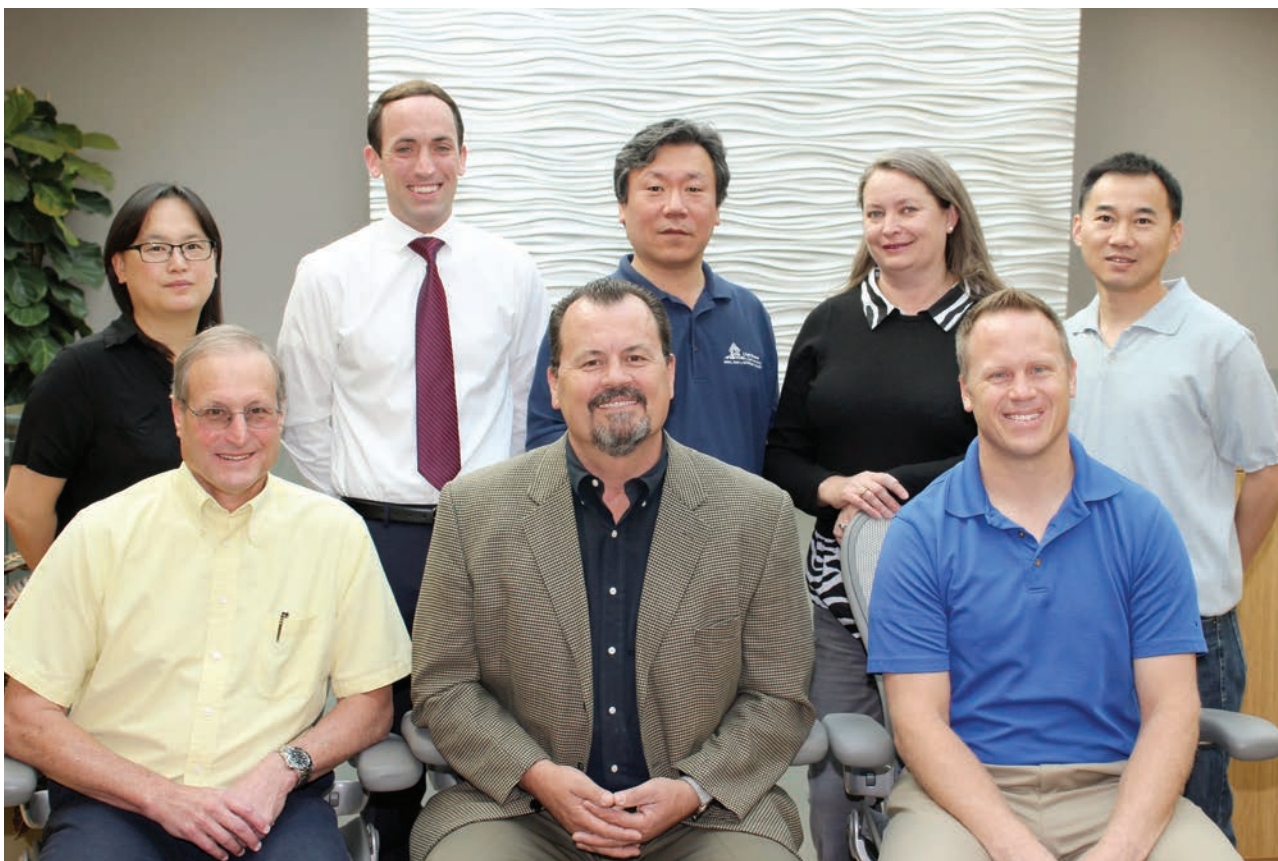
BY DAVID HOLZMAN  
& LYNNETTE HARRIS

A team of researchers at Utah State University has characterized the consensus genome sequences of three historically important Zika virus strains, an important step toward developing antiviral therapeutic and preventive strategies against Zika, and related viruses. The research is published August 18 in *Genome Announcements*, a journal of the American Society for Microbiology.

"The epidemic in the Americas is potentially threatening the entire world," said senior author Young-Min Lee, associate professor in the College of Agriculture

and Applied Sciences' Department of Animal, Dairy and Veterinary Sciences. The new research, he said, may ultimately lead to stopping Zika's spread, and preventing future outbreaks.

Previously, these researchers focused on understanding the molecular basis of viral replication and pathogenesis of the Japanese encephalitis virus (JEV), a mostly neglected but clinically important pathogen, which, like Zika, is a flavivirus. That research has provided a lot of information that will be critical to efforts to tame Zika, said Lee.



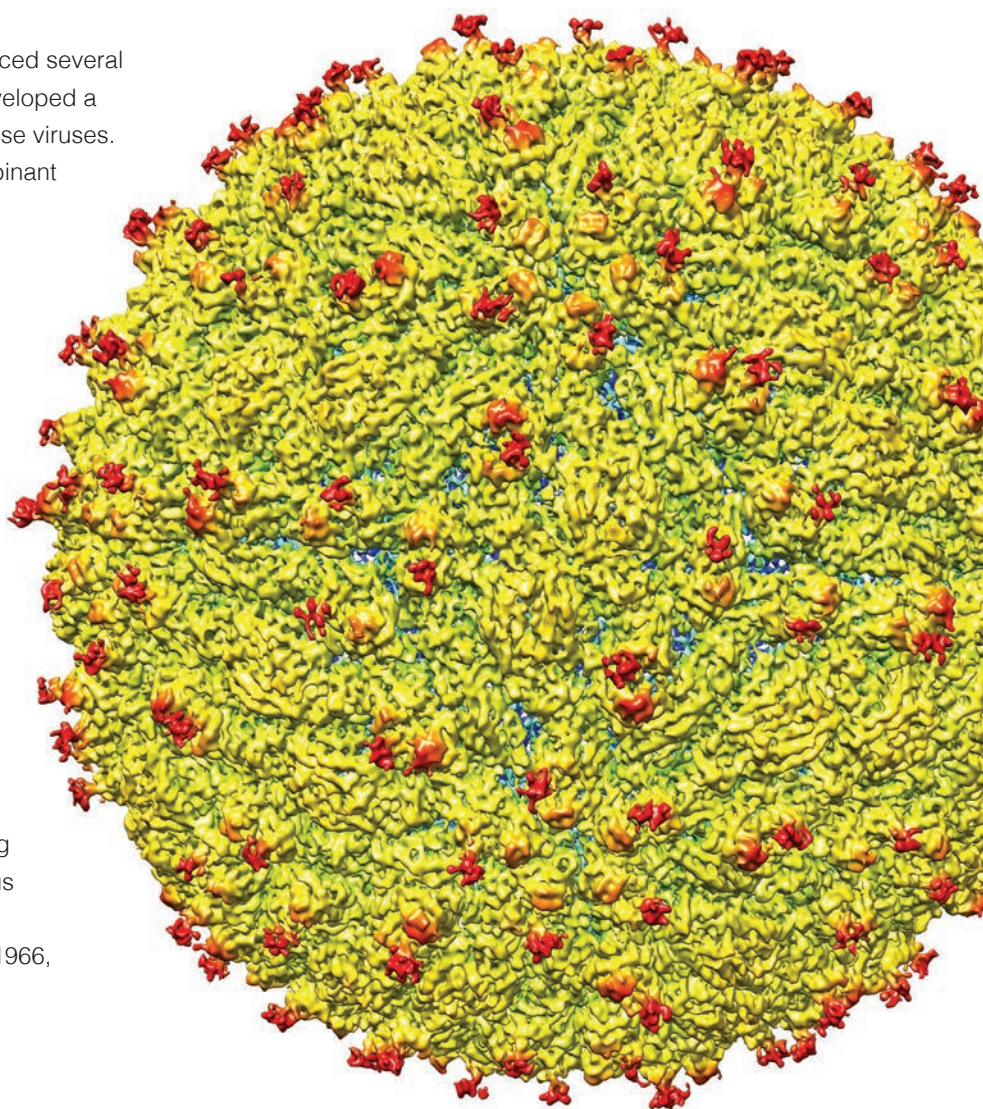
*USU scientists successfully sequenced the genomes of three important strains of Zika virus that will be important tools in the search for treatments and a vaccine against the virus. **Back row, left to right:** Sang-Im Yun, Jordan Frank, Young-Min Lee, Irina Polejaeva and Byung-Hak Song. **Front row:** Chris Davies, Ken White and Justin Julander.*

For example, the researchers had sequenced several clinically important strains of JEV, and had developed a “reverse genetics” system for manipulating those viruses. That system made it possible to create recombinant and mutant JEVs. That, and other tools these investigators developed for JEV can easily be adapted to use on Zika.

These tools will allow them to create an attenuated (less virulent) Zika virus that can serve as a candidate vaccine, said Lee. The researchers can attenuate the virus by inactivating a protein that Zika uses to invade human cells.

The first of the three Zika virus strains whose sequences the researchers have characterized was isolated in 1947, from a sentinel rhesus monkey in Uganda. “A sentinel animal is an animal intentionally placed in a particular environment to detect the presence of an infectious agent in the area,” said Lee. “Zika virus was discovered accidentally in the Zika forest of Uganda during a search for yellow fever virus, another flavivirus related to Zika.”

The second strain of Zika was isolated in 1966,



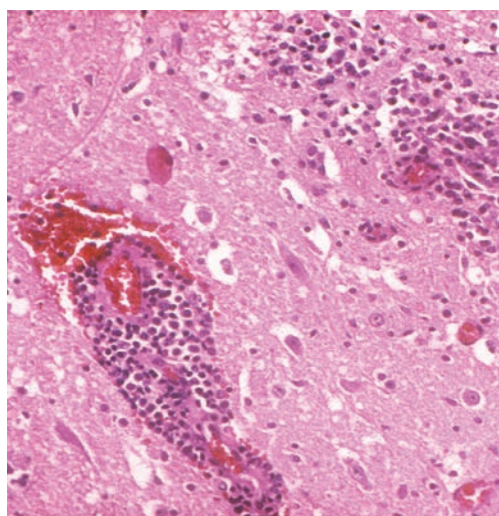


from a pool of *Aedes aegypti* mosquitos in Malaysia. The third strain is responsible for the epidemic that recently swept Latin America. It was first isolated in early 2015, in Puerto Rico, and has now reached Florida, where it has begun to spread.

From this research, and from an analysis using the sequences of 29 available Zika virus genomes, the Utah team has shown that these viruses fall into two major genetic lineages: One African and one Asian. The latter includes both the Malaysian, and the American epidemic strain. That latter strain is derived from an ancestor of the Asian lineage.

Meanwhile, questions remain as to why the strains differentiated. Viruses face different environments in different hosts, said Lee. "The most obvious and significant challenge to the virus is the host immune response, and evasion of the host immune response is a key feature of the survival strategy. Studies are currently underway at Utah State University to examine the functional importance of the genetic variation on viral replication and pathogenesis."

Other contributors to the genome sequencing project and co-authors on the paper are technicians and faculty members in the College of Agriculture and Applied Sciences: Sang-Im Yun, Byung-Hak Song, Jordan Frank, Justin Julander, Irina Polejaeva, Christopher Davies and Kenneth White. ☐



**Left:** Representation of Zika virus. Image courtesy of Kuhn and Rossmann research groups, Purdue University.

**Above:** This photomicrograph revealed some of the histopathologic changes in this specimen of equine brain tissue revealing the perivascular inflammation associated with this West Nile virus (WNV) infection. CDC/A. Wilson; Brian W.J. Mahy, BSc, MA, PhD, ScD, DSc

# TOP 5 THINGS EVERYONE NEEDS TO KNOW ABOUT ZIKA

## 1

**Zika primarily spreads through infected mosquitoes. You can also get Zika through sex.**

Many areas in the United States have the type of mosquitoes that can spread Zika virus. These mosquitoes are aggressive daytime biters and can also bite at night. Also, Zika can be passed through sex from a person who has Zika to his or her sex partners.

## 2

**The best way to prevent Zika is to prevent mosquito bites.**

- Use insect repellent. It works!
- Wear long-sleeved shirts and long pants.
- Stay in places with air conditioning or window and door screens.
- Remove standing water around your home.

## 3

**Zika is linked to birth defects.**

Zika infection during pregnancy can cause a serious birth defect called **microcephaly** that is a sign of incomplete brain development. If you have a partner who lives in or has traveled to an area with Zika, do not have sex, or use condoms every time you have sex during your pregnancy.

## 4

**Pregnant women should not travel to areas with Zika.**

If you must travel to one of these areas, talk to your healthcare provider first and strictly follow steps to prevent mosquito bites during your trip.

## 5

**Returning travelers infected with Zika can spread the virus through mosquito bites.**

If you get infected with Zika and a mosquito bites you, you can pass the virus to the mosquito. The infected mosquito bites other people, who get infected. Returning travelers should also use condoms or not have sex if they are concerned about passing it to their partners through sex.

[WWW.CDC.GOV/ZIKA](http://WWW.CDC.GOV/ZIKA)

CS264222-A August 2, 2016

# synthesis:

## UTAH CLIMATE CENTER HONORED FOR 125 YEARS OF WEATHER DATA

By Lynnette Harris

Scientists at Utah State University have been recording and reporting daily weather observations for 125 years and the Utah Climate Center was recognized by the National Weather Service with an Honored Institution Award for that consistent service and the vast amount of data it has generated.

Accurate weather forecasts are crucial to decisions that affect people, corporations, government entities and entire economies, and those forecasts are built on records of daily weather observations. Each time Utah Climate Center staffers gather information about specific details of the day's weather they are adding more important data points to an unusually long record.

"Long records are very important to helping us understand climate and how things have changed over time," said Randy Graham, meteorologist-in-charge at the National Weather Services' Salt Lake City office. "Back in the day, this was about climatology and establishing our climate record. Now this data is going into numerical weather prediction

models and helps improve our forecasts."

Currently, daily observations are made and recorded by Utah Climate Center employees Martin Schroeder or Boniface Fasu, and occasionally by center director and State Climatologist Robert Gillies. Their work is added to records that include more than 45,600 days-worth of observations. Fasu explained that each day they record daily maximum and minimum air temperatures, precipitation, soil temperatures at four different depths and a description of visibility distances and note whether it's sunny, overcast, windy, raining or snowing. In fact, one of the challenges in documenting the weather is the weather.

"Reading instruments in a blizzard is really interesting," Gillies said. "And once, when a strong inversion had built for several days, I drove past the entrance to one station twice because I couldn't see where to turn off the road."

Lisa Verzella, a National Weather Service meteorologist who coordinates the network of Utah's volunteer observers,

## PROFESSOR HONORED FOR IMPROVING LIVES IN AFRICA

By Shelby Ruud & Lynnette Harris

For more than 30 years Layne Coppock has led highly successful research programs that also change peoples' lives in southern Ethiopia and northern Kenya. His efforts were honored with two prestigious awards, one for career achievement in eastern Africa from a professional organization in Ethiopia, and another from the Board for International Food and Agricultural Development (BIFAD), recognizing the sustained success of a pastoral women's collective-action project initiated in 1999. The work with the pastoral women was part of the USAID-funded

ed Pastoral Risk Management (PARIMA) project at USU from 1997 to 2009.

Coppock, a professor in the Department of Environment and Society and a Utah Agricultural Experiment Station researcher, received the 2015 Scientific Award for Excellence from BIFAD, is a presidentially appointed board that advises the United States Agency for International Development (USAID) concerning links between USAID and U.S. universities.

The project was novel in that the focus was on a



# Science at Utah State



*Utah Climate Center Director Robert Gillies with Randy Graham and Lisa Verzella from the National Weather Service's Salt Lake City office, and climate center staffers Martin Schroeder and Boniface Fasu (left to right).*

said although there are stations with automated sensors, people provide better records because they are familiar with the instruments they use and how they read them. In addition, when a severe weather event occurs and road crews and others need to know about current conditions, automated instruments may not “see” the activity because radar is blocked by mountains.

“But we can contact observers in an area and get a report of what’s really happening on the ground,” Verzella

said. “We often get calls from insurance companies checking on weather events on a specific date when they are evaluating claims.”

Graham said data collected by observers is examined closely after a severe weather event, including information from the days and hours preceding it, to help develop better forecasting tools. Although individuals may think of weather only in terms of how it affects their plans, forecasting is vital to the nation’s economy. ☐

participatory, action-research approach where members of pastoral communities helped co-direct the work. A blend of research, outreach, informal education, and training led thousands of pastoralists—mostly poor, illiterate women—to empower themselves and form self-help groups that saved money, invested wisely in a variety of economic development activities, improved risk management in their households level, and thus helped transform destitute communities.

“The key to success was building human, social, and financial capital—not the implementation of new production



*Colleagues Getachew Gabru and Layne Coppock.*



*Participants in the Pastoral Risk Management project women's program learned new animal management and business skills that improved rangeland ecology and their families' economic well-being.*

technology," Coppock said. "Because the interventions are self-sustaining and easily replicated, the impacts from this project have grown over time."

In 2003 there were 2,300 founding members in 59 groups with a savings and loan volume equal to U.S. \$650,000. By 2015–6 years after the project formally ended—there are 87,000 participants in 795 groups with a savings and loan volume over U.S. \$28 million.

The work of Coppock and his team of Ethiopian and Kenyan colleagues is the first instance of rangeland-focused work being recognized by BIFAD. Members of the team include Coppock, Getachew Gebru, Solomon Desta, Seyoum Tezera, Azeb Yonas, Abdillahi Aboud, Mark Mutinda, and Stellamaris Muthoka.

Coppock was also honored with a career achievement award from the Ethiopian Society of Animal Production. His career in East Africa has included his role in the National Science Foundation-funded South Turkana Ecosystem Project (Kenya) in the 1980s, authorship of a book on Ethiopian rangelands in the mid-1990s, stewardship of the PARIMA project, and his role in Ethiopian land-management research since 2012. After receiving his award, Coppock gave a presentation concerning interactions in Ethiopian pastoral systems that connect livestock production, human health and water quality.

DeeVon Bailey, associate dean for research in the College of Agriculture and Applied Sciences, who formerly oversaw international program development at USU, said Coppock is successful because he works with people at the grassroots level and asks them what they believe would help their situation the most. Then the research, outreach, and training aspects are packaged around those goals.

"I consider his programs, especially the PARIMA pastoral women's program, to be the most successful U.S. university-implemented program I have seen during the almost 20 years I have been working in Africa," Bailey said. "Layne has discovered the key that marginalized, uneducated people are trapped by poverty. They are very talented and thus capable of solving many of their own problems, but they need to be empowered to do so. Empowerment comes from respecting their wisdom, providing guidance, and helping them gain access to the appropriate tools and techniques. Such success does not come from top-down research initiatives." □



# EXPERIMENT STATION GETS NEW ASSOCIATE DIRECTOR

By KailCee Harrison

Chris Davies, research associate professor in the Department of Animal, Dairy and Veterinary Sciences, was recently named associate director of the Utah Agricultural Experiment Station.

Davies received both his Doctor of Veterinary Medicine and PhD from Cornell University. Before joining Utah State University in 2007, he was a researcher and associate professor at Washington State University.

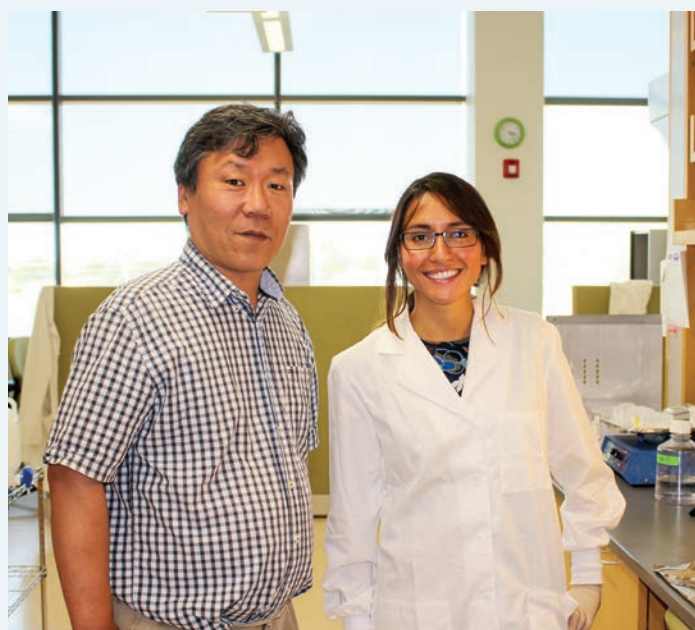
Davies' strong background in animal science research and work with USU's Center for Integrated BioSystems have prepared him for the new position. While working on his undergraduate and graduate degrees he trained horses, worked at the Cornell Dairy and became interested in immunology, which, ultimately led to his career in studying immunogenetics. His research at USU focuses on immune response and gene expression at the maternal-fetal interface, specifically in cattle. Davies is excited to use his research background to further the mission of the Utah Agricultural Experiment Station.

"Utah State University has a strong agricultural research program," Davies said. "We are one of the top Ag schools in the country and I want to continue to build on that success. Part of that is overseeing use of money to strengthen programs and provide core resources for our faculty who conduct research. Many people don't know that although most experiment station researchers are in the College of Agriculture and Applied Sciences, we also support projects in the university's colleges of science, natural resources, education and human services, engineering and in humanities and social sciences."

Davies is assuming the position formerly held by long-time UAES Associate Director Donald Snyder who retired in June. Davies will work to support the Utah Agricultural Experiment Stations mission of generating knowledge and new technology to "improve the diverse system of agriculture and natural resources that feeds, clothes, houses and enhances the environment for Utah's citizens." His primary responsibility will be to manage research funding from the State of Utah and U.S. Department of Agriculture to ensure that it is used and reported on appropriately. ☐



*Research Associate Professor Chris Davies.*

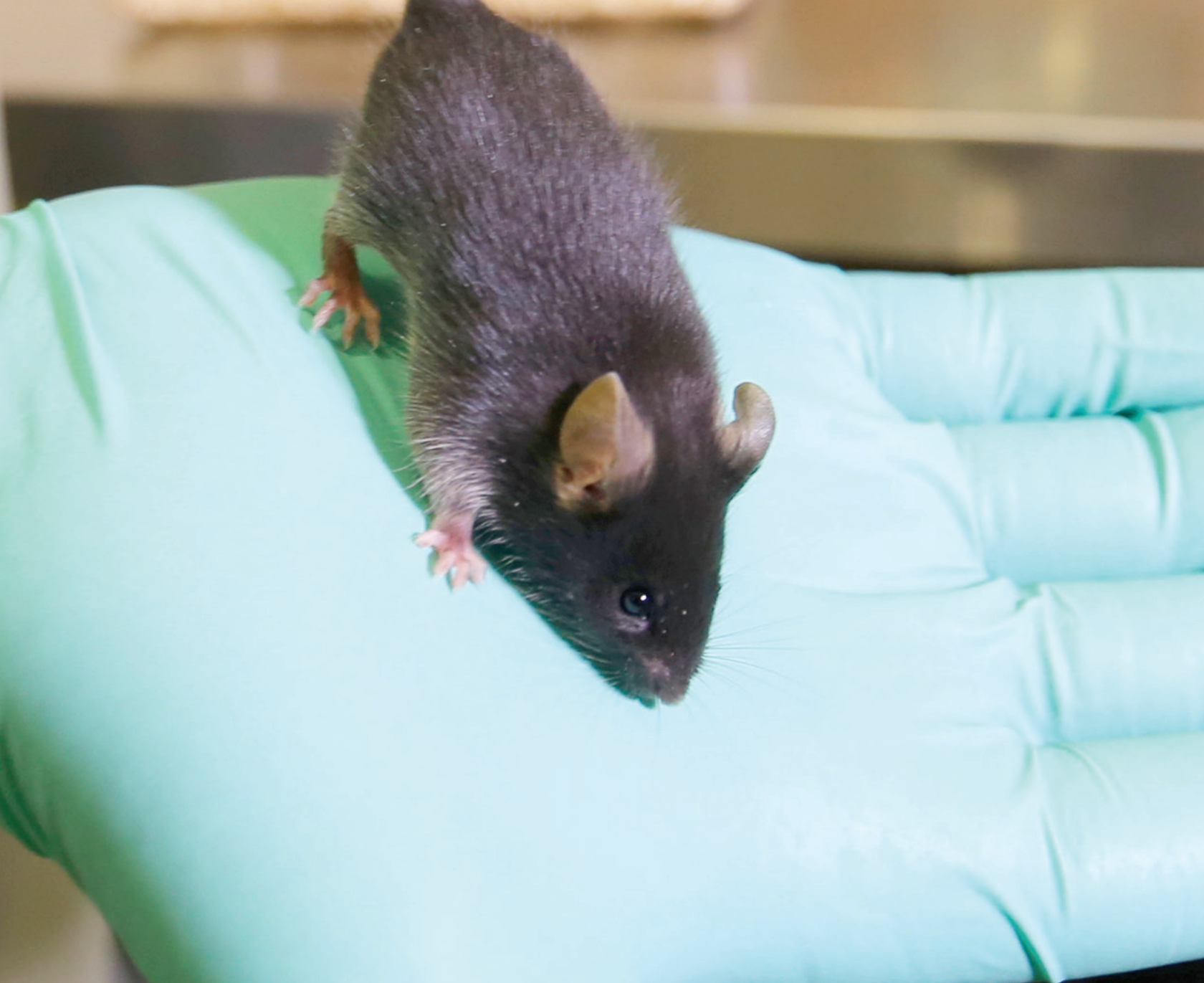


For 10 weeks last summer, nine students from small colleges in Utah and surrounding states worked in research laboratories with USU faculty mentors in the Summer Undergraduate Agricultural Biotechnology Research Experience (SURE). "I think the connections and the experiences that come from this unique program have a lot of potential to change students' career objectives and opportunities," said Chris Davies, the program's co-director.

Students received a stipend for their work improving crop varieties, developing biofuels, studying antiviral drugs and exploring other agricultural and biological problems.

Jackie Bedoya-Wilkinson, a student at Weber State University said, "I never thought I would be able to participate in undergraduate research. I didn't even know how to get started. Now I get to use state-of-the-art equipment to work on important projects every day."

Davies said the SURE program is set to continue for at least the next 2 years with funding from the USDA.



**T**here is an eye-catching photo of a fat mouse and a thin mouse on the flyer soliciting participants for a campus research project. You might conclude that this study is related to diet and exercise, but it isn't. Both mice were fed the same diet; the only variable is the bacteria in their gut. Korry Hintze, a Utah Agricultural Experiment Station researcher and associate professor in Utah State University's Department of Nutrition, Dietetics and Food Sciences, is studying how this could be applied to human health.

"Gut bacteria, or microbiome, has co-evolved along with humans and animals, Hintze said. "Only recently have we been able to understand many of the ways it relates to health. The field exploded because of DNA sequencing. It is an easier and cheaper way to examine bacteria than the old methods of bacteria culturing, and

some bacteria could not be cultured. "

There was a time when we thought all bacteria were harmful and that using antibiotics to kill them would lead to better health, Hintze said. But there are as many as 1,000 species of microorganisms in the human digestive tract, and more recently, scientists are discovering how useful and variable the microbiome is. For instance, Cesarean-delivered babies have a different microbiome than those born vaginally. This is because babies are born pretty much sterile and acquire bacteria from their mothers at delivery. So babies delivered via C-section have a microbiome more analogous to their mother's skin as opposed to the mother's natural gut microbiome.

We also now know that breast feeding plays an important role in both the health of the baby and the



# OUR COMPLICATED RELATIONSHIP WITH THE MICROBIOME

By Dennis Hinkamp

microbiome, Hintze said. Breast milk contains indigestible milk fiber. Because species don't generally develop wasteful adaptations, researchers conclude that a large part of breast milk is not there for the baby; it's there for the newly emerging bacteria in the baby's gut.

Microbiome variability is a proven factor in mouse weight gain. Counterintuitively, the more efficient the bacteria, the greater chance of obesity. Is swapping microbiomes a cure for obesity?



Mice and humans consume food that may not be digestible to them but is digestible to the microbiome, Hintze said. More efficient gut bacteria can convert more of that food to short-chain fatty acids which can be absorbed as added calories. The less efficient bacteria let undigested food pass through as waste.

**“It’s well known that obese mice have microbiomes that are more efficient at making this conversion and returning energy to the host,” Hintze said. “There are, however, a lot of unknowns about how this would work in humans. We are not as reliant on short chain fatty acids. Mice have a fermentation pouch in their digestive system that aids digestion and we don’t.”**

The “Fecal Microbiota Transplant Study” is designed to answer some of these questions, Hintze said. The Center for Human Nutrition Studies will collect fecal samples from lean and obese volunteers. The samples will be homogenized in a saline solution and transferred to the mice through a feeding tube. The mice will then be fed low and high calorie diets and monitored to see if the human microbiome affects their weight gain. Their health, weight and body composition will be examined





to see if the human microbiome characteristics are transferred to the mice.

"This used to be an extremely expensive process because of the difficulty of raising research mice that were bacteria-free," Hintze said. "We have found a quicker, less expensive way of starting the mice off bacteria free. We treat them with antibiotics for 2 weeks prior to the transfers."

Human to human fecal transplants show promise but doctors are proceeding with caution, he said. Microbiome transplants from healthy humans to those infected with clostridium difficile colitis "c-diff" have been 98 percent effective at curing the sometimes deadly bacterial infection that can develop in people, usually in care facilities, who have had long-term antibiotic treatment. Because antibiotics destroy many of the microorganisms that normally keep c-diff bacteria in check, it can grow without competition and release toxins that attack the intestinal lining and can cause life-threatening holes in the intestines or inflammation in the colon.

We shouldn't have to say this, but "don't try this at home," said Janet Bergeson, clinical coordinator at

USU's Center for Human Nutrition Studies. If you search the Internet you will find tutorials on concocting fecal transfer home remedies. The danger is that you don't know what microbiome traits you might be transferring. Certain microbiome characteristics are also associated with diabetes and colon cancer.

Hintze said "probiotics" available as supplements are generally regarded as safe, but there isn't much good research to support the claims that they are effective. If they do work, you must consume them regularly because they don't survive well in the gut.

Studying the microbiome brings into question exactly what we are. There's "us" and also the symbiotic bacteria that live inside us. Hintze said we need to look at ourselves as more of a superorganism rather than us and them. For the health of the superorganism we need to consider the effects of foods and medicines not just on us, but also on the microbiome that coexists with us. 🍌

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**Left:** Undergraduate researchers Niklas Aardema and Ashli Hunter working with mice in the lab.

**Above:** Human nutrition researchers Korry Hintze, Daphne Rodriguez and Janet Bergeson.



# TRANSGENIC GOATS MAY HELP HEAL HEARTS







Scientists from Utah State University and the University of Utah have developed a new animal model to better understand atrial fibrillation, the most common type of heart arrhythmia.

Irena Polejaeva in USU's College of Agriculture and Applied Sciences, and Ravi Ranjan, from the U of U School of Medicine, lead a team of researchers that have created the first transgenic goat model for atrial fibrillation. Their findings were recently published in the Journal of Cardiovascular Electrophysiology.

According to Polejaeva, associate professor in USU's Department of Animal, Dairy and Veterinary Sciences, there are typically two types of models used in cardiology: transgenic mouse models commonly used to understand gene function, and large animal models including pigs, goats and dogs that are not genetically modified.

"What we've done is combine these two approaches," Polejaeva said. "We produced a transgenic large animal model, which makes several conditions much more reproducible because it is similar to a human-sized heart."

Now the researchers are studying the relationship between atrial fibrillation and cardiac fibrosis, the formation of excess fibrous connective tissue in the heart that lowers its functionality. This condition is commonly associated with atrial fibrillation, though the exact relationship is unclear.

Polejaeva said with atrial fibrillation affecting upwards of 2.7 million adults in America and causing an irregular, rapid heartbeat and leading to fainting, chest pain, stroke, heart failure and other health problems, there was a need for a more effective way to study these heart conditions.

"This goat model, that closely and uniquely resembles the human disease, provides a unique platform to study and gain a mechanistic understanding of how fibrosis makes these hearts more susceptible to atrial fibrillation," said Ranjan, doctor and associate professor in the Division of Cardiovascular Medicine and clinical electro physiologist at the U of U.

According to Ranjan, this model will play a key role in developing new drugs, examining device-related treatments, and identifying the best timing and duration of preventative treatments.

The Utah Science Technology and Research Initiative (USTAR), the Utah Agricultural Experiment Station and the American Heart Association currently fund the project.

Other researchers involved in the successful collaboration and co-authors on the report are: Christopher Davies, Misha Regouski, Justin Hall, Aaron Olsen, Quinggang Meng, Heloisa Rutigliano, Aaron Thomas, Rusty Stott, Kip Panter Arnaud VanWettere, John Stevens, Zhongde Wang and Kenneth White at Utah State University; Derek Dosdall, Nathan Angel, Frank Sachse, Thomas Seidel, Rob Macleod and Nassir Marrouche at the University of Utah; Pamela Lee, Washington State University College of Veterinary Medicine.



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**Left:** USU Associate Professor Irena Polejaeva.



# ONE HEALTH AND EMERGING INFECTIOUS DISEASES

By E. Bart Tarbet, Research Associate Professor  
Department of Animal, Dairy and Veterinary Sciences

**F**rom 2010 to 2015, Utah State University's Institute for Antiviral Research and Center for Integrated BioSystems trained personnel from vaccine manufacturers in developing countries in support of the World Health Organization's international vaccine production capacity building program. Through that involvement I became interested in global public health, and teaching microbiology and infectious diseases in the new School of Veterinary Medicine has expanded my interest to global animal health. I have heard it said that we are all

part of a "global village". In our modern world infectious diseases can travel remarkably fast.

Over the last 30 years, approximately 75% of new and emerging human diseases have been zoonotic (meaning a disease transmitted from animals to people), and many have come from wildlife.<sup>1</sup> The Foresight Report describes the projected risks from infectious diseases of humans, animals and plants over 10- and 25-year horizons, and predicts that the highest probability of



emergence will be associated with RNA viruses, especially those found at the human-animal interface.<sup>2</sup> Understanding the mechanisms that underlie newly emerging and reemerging infectious diseases is one of the most difficult scientific problems facing society today. Examples of human disease outbreaks that had their initial transmission from animals include: avian influenza in 1997, Severe Acute Respiratory Syndrome (SARS) in 2003, the novel swine-origin H1N1 strain of influenza A virus in 2009, and Middle East respiratory syndrome (MERS) in 2012.

It is critical for the future control of disease outbreaks to understand and respond appropriately to new and emerging disease threats. This will require a paradigm shift from outbreak response, to predicting the outbreak before it happens. One such approach involves One Health, the emerging discipline that brings together human, animal and environmental health. The first Utah One Health Symposium was held in October 2015, and members of the USU School of Veterinary Medicine played an important role in the success of that event. Another symposium on this new and important topic is set for October 2016.

The essence of One Health is a collaborative, integrated, and multidisciplinary approach to better understand and better address the challenges and threats of infectious diseases to humans and animals. This approach will require infectious disease experts, physicians, veterinarians and environmental scientists to collaborate and identify the underlying drivers of disease emergence and develop interventions that prevent the transmission of disease. We need to understand the conditions that allow diseases to emerge and spread due to increased population density in cities, increased use of intensive farming practices, and increased travel globally. In addition, we must learn from recent experiences, and move from a crisis-driven society to one of prevention and preparedness.

One Health as a concept embraces disease ecology, and contributes to a better understanding of emerging disease dynamics and the interdependence between human, animal and environmental health in addressing emerging disease threats. □

Bart Tarbet began his training in infectious diseases (medical microbiology) at the Louisiana State University Medical Center in 1992. He worked for 12 years in the vaccine industry and developed veterinary vaccines to emerging (West Nile Virus) and reemerging (influenza virus) diseases in multiple species of animals. At the USU Institute for Antiviral Research, his research in human and animal infectious diseases has merged into developing animal models of human infectious disease for evaluation of experimental therapeutics and vaccines.

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#### **ON THE BACK COVER**

*3D computer-generated image of a group of methicillin-resistant Staphylococcus aureus (MRSA) bacteria. U.S. Centers for Disease Control and Prevention - Medical Illustrator.*

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